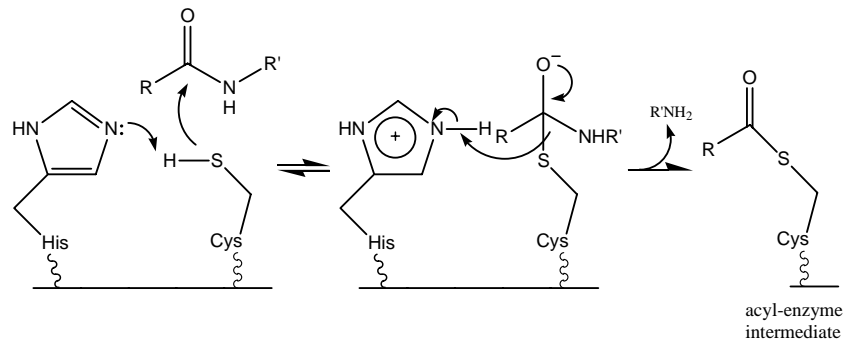


Introduction to Cathepsins

Cathepsins are a class of globular lysosomal proteases, most of which contain an active-site cysteine residue. This nomenclature initially described any group of intracellular peptide hydrolases, although several cathepsins also have extracellular roles. A main physiological role for cathepsins is general protein turnover in the lysosome. This role is exploited in the antigen presentation function of the immune system. Additionally, when cathepsins are directed to the outside of the cell, they can degrade proteins in the extracellular matrix. Tumor cells will secrete cathepsins so that the extracellular matrix can be degraded thus assisting the metastasis of the tumor. In fact, a clinical test for the increased progression of a cancer is elevated plasma levels of cathepsins B and L.

When the single polypeptide cathepsins are first translated they contain an additional sequence of amino acids called the propiece. The propiece physically blocks the active site of the enzyme, effectively making it inactive. Once the cathepsin reaches the acidic environment of the lysosome, the propiece loses its structure and is cleaved from the enzyme, revealing the mature, active cathepsin. Whether the propiece is cleaved autocatalytically or by another cathepsin enzyme depends on the type of cathepsin.

Most cathepsins contain an active-site cysteine residue that acts as a nucleophile and a histidine residue that acts as a general base in the hydrolysis of a target peptide bond in the substrate (see figure). For example, in cathepsin B Cys₂₉ and His₁₉₉ are the active-site residues. Specific inhibitors of cathepsins take this mechanism into account.



The cathepsins have broad specificity albeit some prefer certain amino acids over others in the target sequence. Additionally, while most are endopeptidases (cleaving peptide bonds within the target sequence), a few are carboxy or aminopeptidases (cleaving the peptide bond at only the carboxy- or amino-terminal residue). For example, cathepsin B is a dipeptidyl carboxypeptidase because it cleaves the last two carboxy-terminal amino acids off the target substrate. Moreover, the enzyme subsites (S) of cathepsin B prefer an arginine (Arg) at the P2 position, a large hydrophobic residue at the P1' position, but not a phenylalanine (Phe) at the P1 position of the peptide/protein substrate (see figure for explanation of subsites, etc. for a general enzyme). The amino acids are numbered such that the peptide bond cleaved is between P1 and P1'.

